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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,536	09/03/2004	Kousuke Tani	Q83408	1208

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EXAMINER	
CHUNG, SUSANNAH LEE	
ART UNIT	PAPER NUMBER
1626	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/22/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,536	TANI ET AL.	
	Examiner	Art Unit	
	Susannah Chung	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 18-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 18-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/3/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 and 18-21 are pending in the instant application. Claims 2-17 have been canceled by supplemental amendment filed on 11/6/2006.

Priority

This application is a 371 of PCT/JP03/02478, filed 03/04/2003.

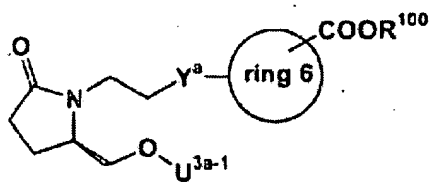
Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) by application nos. 2002-58487, 2002-216567, and 2003-13447 filed in the Japanese Patent Office on 3/5/2002, 7/25/2002, and 1/22/2002, which papers have been placed of record in the file. The application names an inventor or inventors named in the prior application.

Information Disclosure Statement

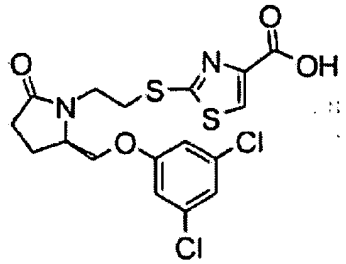
The information disclosure statement (IDS), filed on 9/3/2004 has been considered. Please refer to Applicant's copy of the 1449 submitted herewith.

Response to Election/Restrictions

Applicant's election without traverse of a new group comprising claims 1 and 18-21, directed to compounds and methods of using the compound of formula (I-a1-1),



, in the reply filed on 11/06/2006 is acknowledged. See page 24 of the original specification for this compound. The election of species for search purposes of



the compound of Example 6(32) of the specification, , is acknowledged.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

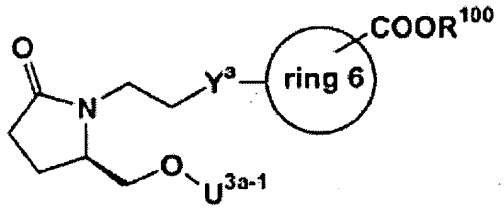
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 18, 19, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cameron et al., U.S. Pat. No. 6,552,067.

Applicants instant elected invention teaches the compound of formula (I-a1-1),



, depicted in claim 1, wherein:

Y^a is -S- or $-SO_2-$;

ring6 is 5 or 6 membered mono-heterocyclic aryl containing hetero atoms selected from 1 to 4 nitrogen, 1 to 2 oxygen, and/or 1 to 2 sulfur atoms which may be partially or fully saturated;

R^{100} is a hydrogen atom or C1-4 alkyl;

U^{3a-1} is ring4;

ring 4 is C3-15 mono-, bi- or tri-carbocyclic aryl which may be partially or fully saturated;

ring4 may be substituted by 1 to 5 R;

R is (1) C1-10 alkyl, (2) C2-10 alkenyl, (3) C2-10 alkynyl, (4) C1-10 alkoxy, (5) C1-10 alkylthio, (6) halogen, (7) hydroxy, (8) nitro, (9) $-NR^{15}R^{16}$, (10) C1-10 alkyl substituted by C1-10 alkoxy, (11) C1-10 alkyl substituted by 1 to 3 halogen atom(s), (12) C1-10 alkyl substituted by C1-10 alkoxy substituted by 1 to 3 halogen atom(s), (13) C1-10 alkyl substituted by $-NR^{15}R^{16}$, (14) ring5, (15) -O-ring5, (16) C1-10 alkyl substituted by ring5, (17) C2-10 alkenyl substituted by ring5, (18) C2-10 alkynyl substituted by ring5, (19) C1-10 alkoxy substituted by ring5, (20) C1-10 alkyl substituted by -O-ring5, (21) $COOR^{17}$, (22) C1-10 alkoxy substituted by 1 to 4 halogen atom(s), (23) formyl, (24) C1-10 alkyl substituted by hydroxy or (25) C2-10 acyl;

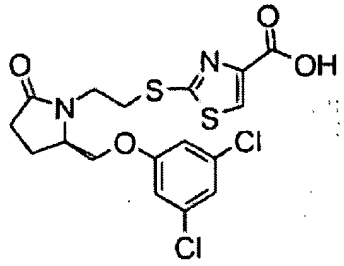
R^{15}, R^{16} and R^{17} are, each independently, (1) a hydrogen atom or (2) C1-10 alkyl;

(1) C3-15 mono-, bi- or tri-carbocyclic aryl which may be partially or fully saturated or (2) 3- to 15-membered mono-, bi- or tri-heterocyclic aryl which may be partially or fully saturated and contains a hetero atom(s) selected from 1 to 4 nitrogen, 1 to 2 oxygen and/or 1 to 2 sulfur atom(s);

(1) C1-10 alkyl, (2) C2-10 alkenyl, (3) C2-10 alkynyl, (4) C1-10 alkoxy, (5) C1-10 alkyl substituted by C1-10 alkoxy, (6) halogen atom, (7) hydroxy, (8) C1-10 alkyl substituted by 1 to 3 halogen atom(s), (9) C1-10 alkyl substituted by C1-10 alkoxy substituted by 1 to 3 halogen atom(s); ~~and~~

a pharmaceutically acceptable salt thereof or a cyclodextrin clathrate thereof.

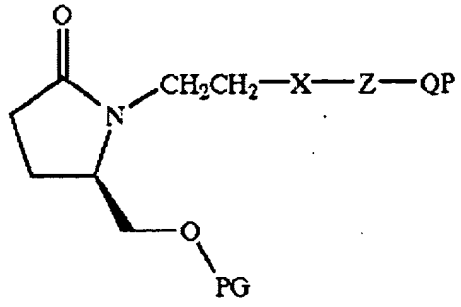
Yielding the elected compound of Example 6(32) of the specification,



, 2-((2-((R)-2-((3,5-dichlorophenoxy)methyl)-5-oxopyrrolidin-1-yl)ethyl)sulfanyl)thiazole-4-carboxylic acid.

Determination of the scope and content of the prior art (MPEP § 2141.01)

Cameron teaches EP4 receptor selective prostaglandin agonists of formula (2),



, wherein PG is a protecting group, which can be benzyl; X is

CH2 or O; Z is thienyl and QP is carboxylic acid, i.e. 2-(3-((R)-2-oxo-5-(phenoxymethyl)pyrrolidin-1-yl)propyl)thiazole-4-carboxylic acid. (See US 6,552,067, Column 15, lines 10-20, 25-27, 39, and 50-54 and column 16, lines 45-47).

Ascertainment of the difference between the prior art and the claims (MPEP § 2141.02)

The difference between the prior art of Cameron, formula (2), and the instant claims is that in the prior art X is CH2 or O, while in the instant application X is S or SO2.

Finding of prima facie obviousness – rationale and motivation (MPEP § 2142-2413)

However, in the absence of showing unobvious results, it would have been obvious to one of ordinary skill in the art at the time of the invention when faced with Cameron to make products useful as prostaglandin antagonists, wherein 2-(3-((R)-2-oxo-5-(phenoxymethyl)pyrrolidin-1-yl)propyl)thiazole-4-carboxylic acid is 2-((2-((R)-2-oxo-5-(phenoxymethyl)pyrrolidin-1-yl)ethyl)sulfanyl)thiazole-4-carboxylic acid.

Guided by the teaching of Cameron one skilled in the art would be able to make similar prostaglandin antagonist compounds by substituting sulfur for oxygen. Sulfur and oxygen are well known bioisosteres of one another. (See Patani et al., Bioisosterism: A Rational Approach in Drug Design, Chem. Rev. 1996, 96, 3147-3176, especially page 3156, which shows that sulfur and oxygen have similar bioactivity.) In view of the similar activity of sulfur and oxygen, the replacement of sulfur for oxygen would be obvious to one of ordinary skill in the art. The motivation would be to prepare similar compounds that are pharmacologically active as prostaglandin antagonists.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 20 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the specification it does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claim, i.e. to treat dysmenorrheal and retinal neuropathy.

As stated in MPEP 2164.01(a), "there are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

The factors to be considered when determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, were described in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as:

1. the nature of the invention;
2. the breadth of the claims;
3. the state of the prior art;
4. the relative skill of those in the art;
5. the predictability or unpredictability of the art;
6. the amount of direction or guidance presented [by the inventor];
7. the presence or absence of working examples; and
8. the quantity of experimentation necessary [to make and/or use the invention].

The eight Wands factors are applied to Claim 20 of the present invention below:

(1) The Nature of the Invention

Claim 20 is directed to a method for preventing and/or treating dysmenorrheal and retinal neuropathy using the compound of claim 1.

(2) The Breadth of the claims

Claim 20 will be give its broadest reasonable interpretation. The applicable rule for interpreting the claims is that "each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." See MPEP 2163(II)(1), citing In re Morris, 127 F.3d 1048, 1053-1054; 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). In view of this rule, Claim 20 will be interpreted to encompass all disorders which could fall into the broad category of retinal neuropathy, as well as the disorder of dysmenorrheal.

(3) The state of the prior art

It was known in the art at the time of this application that similar pyrrolidinone compounds can act as EP4 receptor selective prostaglandin antagonists. (See U.S. Pat. No. 6,552,067 B2). The compounds of the instant application have been known to treat osteoporosis and other related disorders. The compounds in the prior art have been tested using ovariectomized (OVX) rat models, a model for postmenopausal osteoporosis.

(4) The relative skill of those in the art

The level of skill in the art (pharmaceutical chemists, physicians) would be high.

(5) The predictability or unpredictability of the art

It is noted that the pharmaceutical art generally is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement varies inversely with the degree of unpredictability in the factors involved. In re Fisher, 427 F.2d 833, 839. Therefore, the more unpredictable an area, the more specific enablement is needed in order to satisfy the statute. Added to the unpredictability of the art itself is the question whether one compound, for example the compound of formula (I-a1-1) of claim

1, could reliably and predictably be extrapolated to treat dysmenorrheal and retinal neuropathy. The state of the prior art at this time dictates that there is no predictability that the instantly claimed compounds could treat dysmenorrheal or retinal neuropathy, even in view of the high level of skill in the art.

(6) The amount of direction or guidance presented (by the inventor)

The specification in the present invention discloses that the compound of formula (I-a1-1) of claim 1 can treat dysmenorrheal or retinal neuropathy, but provides no biological data supporting this assertion. The state of the art of the instantly claimed compounds states it can treat osteoporosis and other related diseases in post-menopausal patients, but does not provide data for the treatment of pre-menopausal patients or patients with eye disorders.

(7) The presence or absence of working examples

As noted in the previous section, the specification discloses that the compound of formula (I) of claim 1 can treat certain dysmenorrheal and retinal neuropathy. However, the specification has no working examples, such as in vivo or in vitro studies of the role the compound of formula (I-a1-1) of claim 1 plays in the treatment.

Further, Applicant did not provide support, such as journal articles or papers, which would demonstrate the effectiveness of the compound of formula (I-a1-1) of claim 1 in the treatment of diseases. The state of the prior art does not show that one compound could effectively treat the diseases claimed in the instant application. Therefore, working examples and test data is crucial to support Applicants claim that the compound of formula (I-a1-1) of claim 1 can indeed treat dysmenorrheal and retinal neuropathy.

(8) The quantity of experimentation necessary (to make and/or use the invention)

Given the absence of direction or guidance (or working examples) in the specification for the role of the compound of formula (I-a1-1) of claim 1 in treating dysmenorrheal and retinal neuropathy, it would cause a skilled artisan an undue amount of experimentation to practice this invention to determine which patients with which diseases would benefit from which of the claimed compounds within the scope of the invention with a reasonable expectation of success.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susannah Chung whose telephone number is (571) 272-6098. The examiner can normally be reached on M-F, 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Date: 12 December 2006